AD_____

CONTRACT NO: DAMD17-91-C-1076

TITLE: NIFEDIPINE FOR TREATMENT OF HIGH ALTITUDE PULMONARY EDEMA

PRINCIPAL INVESTIGATOR: Peter H. Hackett, M.D.
AUTHORS: R.C. Roach, E.R. Greene, B. Levine

CONTRACTING ORGANIZATION: Denali Medical Research Project
1200 Airport Heights, Suite 320
Anchorage, Alaska 99508

REPORT DATE: July 30, 1992

TYPE OF REPORT: Final Report

PREPARED FOR: U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	30 July 1992	Final Report (5/1/91 - 9/30/92)

4. TITLE AND SUBTITLE
Nifedipine for Treatment of High Altitude Pulmonary Edema

5. FUNDING NUMBERS
Contract No.
DAMD17-91-C-1076

61102A
3M161102BS15.CA.062
WUDA335868

6. AUTHOR(S)
Hackett, Peter H.; Roach, R.C.; Greene, E.R.; Levine, B.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Denali Medical Research Project
1200 Airport Heights, Suite 320
Anchorage, Alaska 99508

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research & Development Command
Fort Detrick
Frederick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

In 12 subjects with high altitude pulmonary edema, we studied the effects of 10mg nifedipine on pulmonary and systemic hemodynamics and arterial oxygen saturation. In five of these, repeated dosing was done over 3 hours and spirometry and clinical HAPE scores were also obtained. A single 10mg nifedipine dose lowered pulmonary vascular resistance and pulmonary arterial pressures, as well as systemic arterial pressure and increased SaO_2%. Multiple dosing sustained the drug effect, but with a smaller increase in SaO_2%. Clinical scores improved slightly, and within 3 hours there was no consistent effect on spirometry. In addition, we undertook a survey of pulmonary hypertension (PHT) at high altitude, and surprisingly discovered excessive PHT in asymptomatic individuals. We conclude that nifedipine vasodilates the pulmonary bed in persons with HAPE, and that this appears to be beneficial, although short-term improvement was minimal. Since asymptomatic PHT is common, factors other than PHT are critical in HAPE pathogenesis, and by extension, could be important in prevention and treatment.

14. SUBJECT TERMS
Altitude, High Altitude Pulmonary Edema, HAPE, Nifedipine, Hypoxic Pulmonary Hypertension, RA III, Volunteers

15. NUMBER OF PAGES

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unclassified

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

( ) Where copyrighted material is quoted, permission has been obtained to use such material.

( ) Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

( ) Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

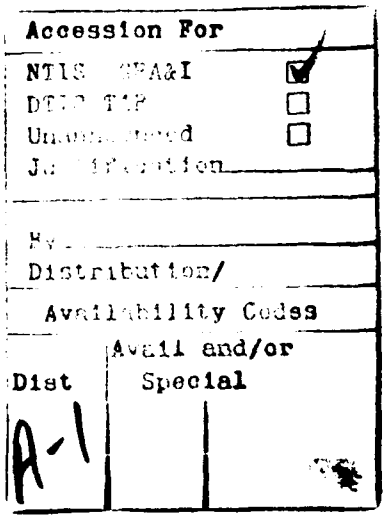
( ) In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

(PH) For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45 CFR 46.

( ) In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

Peter N Hackett MD 6-20-92

PI Signature Date



Personnel Receiving Pay

Peter Hackett, M.D. , principal investigator

Glenn Hartig, M.S., research assistant

Rob Roach, M.S., consultant

TABLE OF CONTENTS

INTRODUCTION

High altitude pulmonary edema (HAPE) remains a serious life-threatening illness in 1 to 2% of persons rapidly ascending to altitudes above 3,000 to 4,000 meters. Incidence varies with rate of ascent and the altitude, while contributing factors include exertion, cold, and most importantly, individual susceptibility.[1] Effective medical treatment in the often remote and rugged settings in which HAPE occurs may be difficult. Descent is often not possible, and oxygen is usually not available, or available in insufficient quantity. An effective medical treatment for HAPE would be of great value to civilian and military populations.

The approach to a therapeutic agent for high altitude pulmonary edema must be based on an understanding of pathophysiology. Numerous studies have suggested that pulmonary hypertension is a critical factor in the development of HAPE, although it is still not clear if the hypertension is cause or effect. Hemodynamic measurements have clearly established that pulmonary hypertension is present in all cases of HAPE.[2] In addition, studies with HAPE susceptibles have shown that the hypertension precedes the development of edema.[3] Others have suggested that a vascular leak takes place first, and that pulmonary hypertension follows.[4] Whether pulmonary hypertension is *a priori* causal or contributes secondarily, it appears to be an essential ingredient in the pathophysiology of HAPE. Therefore, vasodilation of the pulmonary circulation may be a rational approach to the treatment of high altitude pulmonary edema.

The underlying cause of the vasoconstriction may dictate the agent most likely to be a successful vasodilator of the pulmonary vascular bed. The pulmonary hypertension of HAPE is reduced 30 to 50% by administration of

oxygen, although not completely, indicating the significant role of hypoxic vasoconstriction.[5,6] Since hypoxic vasoconstriction is thought to be a calcium dependent smooth muscle contraction, calcium entry blockers may well prevent this constriction. Previous studies in normal persons have indicated a nearly universal effect of nifedipine on blunting the hypoxic vasoconstriction response. Oelz et al[7] and Hackett et al[6], in preliminary studies, described benefit from use of nifedipine. They reported a drop in pulmonary artery pressure of 30 to 40% in subjects with HAPE, and also a slight increase in arterial oxygenation. We wished to extend these observations by studying the effects of nifedipine on hemodynamics and oxygenation in a larger number of HAPE subjects. In addition, we wished to examine the effectiveness of repeated doses of nifedipine, and determine the safety of the drug in a field setting.

Accordingly, using noninvasive Doppler echocardiography, we performed two series of experiments at our laboratory on Mt. McKinley, and also at a moderate altitude ski resort in Colorado. Our study of single-dose nifedipine in twelve subjects with HAPE indicated that 10mg nifedipine significantly reduced pulmonary artery pressure and pulmonary vascular resistance, reduced systemic arterial pressure, and improved arterial oxygenation. The effect, however, was for less than 30 minutes. With repeated dosing in a smaller group of five of these subjects, nifedipine continued to exert an effect on pulmonary artery pressure, and arterial pressure, with a small improvement in symptom score and little effect on oxygen saturation. These results suggest a critical role for pulmonary hypertension in the pathophysiology of HAPE, and confirm the potential usefulness of vasodilators. Postural hypotension developed in some subjects, and may limit the use of nifedipine in large dosages.

BODY

Experimental Design and Methods

All studies were completed either in the laboratory at 4,300 meters (barometric pressure 440±4 torr) on the West Buttress of Denali, or in a portable laboratory in Keystone, Colorado, at 2835m, barometric pressure 538±4.2 torr). Both laboratories were heated with a propane heater to maintain room temperature near 20°C.

Of the 12 subjects with HAPE eleven were males; average age was 34 ±4 years. HAPE was diagnosed by the presence of the following major symptoms: dyspnea on exertion, weakness, rales, exaggerated arterial oxygen desaturation (normal at 4,200 m = 84% ± 2%, and at 2835m = 91%±2%), and the absence of any other illness. Minor criteria included tachycardia, tachypnea, and dyspnea at rest. Chest radiographs when available confirmed pulmonary edema. The study was explained in detail to all volunteers, and informed consent obtained.

Measurements and clinical assessment

Baseline measurements included heart rate, respiratory rate, arterial oxygen saturation by pulse oximeter (Criticare Systems model #503), auscultation of all lung fields, and systemic blood pressure both supine and standing. Forced vital capacity, peak expiratory flow rate and a score for severity of HAPE was obtained for the extended study (see appendix for HAPE score). A brief clinical neurological assessment was also performed, noting level of consciousness and presence or absence of ataxia. Patients with encephalopathy were either not enlisted in the study, or studied after sufficient recovery so that mental status was normal without supplemental oxygen.

We estimated pulmonary artery pressure and cardiac output using Doppler echocardiographic technique. Systemic and pulmonary vascular resistances were calculated from measured cardiac output and mean arterial pressure, and estimated pulmonary artery pressure, respectively. Cardiac output was measured at baseline and fifteen minutes only.

Noninvasive measurements

We used a 3 MHz Doppler echocardiograph, the Hewlett Packard Sonos 100, whose general theoretical and technical characteristics have been described previously in detail.[8] Basically, the system combined a 90-degree two-dimensional mechanical sector scanner with a pulsed Doppler velocimeter and a fast Fourier transform spectrum analyzer. An IBM-PC computer and digitizer pad was used for signal processing. All noninvasive measurements were obtained with the scan head placed in the second or third intercostal space along the left sternal border. The scan plane was aimed laterally and superiorly to obtain a standard short axis view of the base of the heart. The right ventricular outflow tract was used to take blood velocity and diameter measurements. Optimal images and Doppler spectral waveforms (**vf**) were recorded at a paper speed of 100mm/sec. To obtain the lumen diameter (**D**), we used calipers to measure (to the nearest 0.1 cm) the distance between the inner walls of the right ventricular outflow tract. A protractor was used to measure (to the nearest degree) the Doppler angle (**R**) from the images. From previous studies the inter-observer variabilities for **D** and (**R**) were less than 7% in our laboratory when compared to the mean values.

Calculated variables

A single observer calculated and averaged ($\pm$SD), from five consecutive cardiac cycles, the ratio (**A**) of the acceleration time (AT

measured in milliseconds from the onset of flow until the peak flow velocity is reached) to the right ventricular ejection time (ET). The outer envelopes of the same 32 dB spectral waveforms were digitized, and the microcomputer used the values of **D** and (**R**) to calculate and average (±SD) the temporal average blood velocities (**V**) from the Doppler equation:

$$V = vf \cdot C / 2 \cdot F \cdot \cos R \ \text{(cm/sec)}$$

where **C** is the velocity of sound in the body (1540 m/sec) and F is the transmitted frequency (3 MHz). Volumetric flow rates (**Q**) were calculated from the continuity equation:

$$Q = P \cdot D^2 \cdot V \cdot 60 / 4 \cdot 1000 \ \text{(l/min)}$$

The coefficients of variation of three independent determinations by a single observer of **A**, **V**, and **Q** were 8%, 9%, and 11%, respectively.

Estimated MPAP

Using results from a previous validation study in our laboratory,[8] we estimated mean pulmonary artery pressure (**MPAP**) from the calculated AT:ET ratio (A) by the equation: **MPAP** mm Hg= 87-152(**A**).

Protocol

Series one

In series one, subjects received a single dose of 10mg nifedipine at time zero, after baseline measurements. The capsule was pierced with a needle, the subjects chewed the capsule and then swallowed it. Measurements were repeated 15 minutes after the capsule was given.

Series two

In the second series, five of the same twelve HAPE subjects received repeated doses of nifedipine, given in the same chew and swallow manner. The protocol called for repeat dosing every thirty minutes, depending upon the blood pressure response of the individual; specifically, a repeat dose was

withheld for thirty minutes if postural hypotension (drop in systolic pressure of greater than 20mm Hg) were present. Over the one hundred eighty minutes, one subject received the full 60 mg (10mg every 30 minutes), three received 40mg, and one consumed 50 mg. Severity score for HAPE was assigned at 30, 60, 120 and 180 minutes. In addition, measurements of At/Et (MPAP) and SaO_2% were done every minute from minute 5 to minute 15, in order to determine the time relationship between change in MPAP and change in oxygen saturation.

RESULTS

Series one

Individual data for the single dose nifedipine trial ARE given in figures one through three; mean data ARE presented in Table 1. Fifteen minutes after the medication, pulmonary vascular resistance and pulmonary artery pressure decreased, systemic vascular resistance and mean arterial pressure were reduced, and arterial oxygen saturation increased a mean of $8.7 \pm 9\%$. The hemodynamic response to nifedipine was rather uniform, despite widely differing body weights. Although there was a trend for those with the highest mean pulmonary artery pressure to have the greatest response to nifedipine, this did not reach statistical significance (fig. 4, top). Mean systemic arterial presure for the group decreased from 98 ± 3mmHg to 89.3 ± 2.5mmHg, $p < 0.01$, while the subjects were supine. Despite a wide range of hydration state, no subject became symptomatic from postural hypotension upon standing. Cardiac output increased in seven of the twelve subjects; the change was significant for the entire group, although the slight increases in heart rate and stroke volume were not significant (Fig.3).

No adverse side effects were noted with the single dose of nifedipine. Four of twelve had a decrease of systolic blood pressure $\geq$ 10mm Hg, but

none ≥ 20mm Hg. The slight postural blood pressure change did not produce symptoms.

Series two

Data for the five subjects for every fifteen minutes of the three hour study are presented in Figure 5 and Tables 2 and 3. Pulmonary pressure measurements were not available on one of the five subjects for six of the data collection times; none of his pulmonary pressure values are included. Pulmonary artery pressure was significantly reduced at 15 minutes and remained lower with repeated dosing for the length of the study. The decrease in MPAP was highly correlated with the pre-treatment pressure(Fig. 4b). Arterial oxygen saturation was not significantly increased, although there was a slight rise with time ($p = 0.06$). Systemic mean arterial blood pressure reached the lowest values after the first dose, and after a period of fluctuation, remained significantly lower than baseline. The main reason for this fluctuation was that four of the five subjects developed postural hypotension (fall in systolic pressure of greater than 20mm Hg) which delayed the repeat dose of 10mg for 30 minutes each time, even though subjects were not symptomatic. This occurred once in one subject, and twice in three subjects, so that total dosage varied from 60mg to 40mg over the three hour period. Postural hypotension was most pronounced in the smallest subject (56kg), and was absent entirely in the largest subject (90kg), despite 60mg over 180 minutes. Symptom scores were lower at 30 minutes, primarily because of reduced sensation of dypnea, and decreased rales. Symptom score started to increase at 180 minutes, but did not reach pretreatment values.

The time to significant drop in pulmonary artery pressure for the four subjects was 8, 8, 15, and 10 minutes. For these same subjects, and in the

same order, the time that arterial oxygen saturation increased was 150 minutes (after the fourth dose), 135 minutes (also after the fourth dose), no improvement at any time, and an increase at 30 minutes. In all subjects, pulmonary pressure decreased well before any increase in oxygen saturation, and there was no apparent relationship between the time course of the changes. When the subjects were analyzed individually, there was a significant but weak correlation between SaO_2% values and pulmonary artery pressure in three of the four: $p<0.05$, $r=-0.38$; $p<0.05$, $r=-0.38$; $p<0.05$, $r=-0.36$.

Spirometry data were available on five subjects, and are given in Table 3. Peak flow decreased 6% in one subject, increased 6% in another, and was unchanged in three. Forced vital capacity was low at baseline, decreased in two subjects (27 and 12% decreases), improved 30% in one other subject, and was unchanged in the remaining two persons. Peak flow and vital capacity changed in the same direction in four of the five subjects, and divergently in the other.

Screening for pulmonary hypertension

In addition to the planned studies, a survey of pulmonary hypertension was accomplished at the 4300m camp on Mt McKinley. Subjects were six HAPE patients, plus expedition groups recruited on random days; some had AMS, most were acclimitizing well. The results are given in Figure 6, in the Appendix. The data demonstrate a nearly normal distribution of values for mean pulmonary artery pressure amongst the 59 subjects studied by doppler echocardiography. Six of these subjects had high altitude pulmonary edema, and were in the two columns with the highest values. Nine other subjects (15%) had values in this range also, but without HAPE at the time of study, and did not go on to develop HAPE.

DISCUSSION

The main findings of this study were that nifedipine vasodilated the pulmonary vasculature in subjects with high altitude pulmonary edema, that the effect were maintained by repeat dosing over three hours, and that although well tolerated, postural hypotension did develop. Vasodilating the pulmonary bed resulted in a small increase in arterial oxygenation and a small decrease in symptom score. In addition, we found unexpectedly high pulmonary artery pressures in entirely asymptomatic subjects at altitude.

We were able to accomplish most of the goals as stated in the contract Statement of Work in the original proposal submitted in 1989 (page 15 of proposal). Due to the war in Kuwait, we had to change location of part of the study to Keystone, Colorado. We had hoped to study ten subjects, and actually studied twelve. We dropped the placebo arm of the study because the intial pilot study clearly indicated no placebo effect, and because many of these subjects were sufficiently ill to raise concerns about giving them placebo, although not so ill that immediate descent was necessary. We had hoped to make measurements of A-a gradients, but the blood gas analyzer failed, and these were not possible. We did determine the effectiveness of repeated doses of nifedipine in HAPE subjects, and we did examine the incidence and severity of hypotension with the drug in this setting. Also, in addition to the stated work, we undertook a survey of pulmonary artery pressure in a very large number of subjects, which provided new and important information.

This work represents the largest series to date on the use of nifedipine in the treatment of HAPE. We extended our previous observations on six HAPE patients from 1988, and extended the dosage and duration of therapy in this new group of subjects. Although the studies were performed at two

different altitudes, the degree of pulmonary hypertension and arterial oxygen desaturation were similar, indicating that the disease process, rather than alveolar PO_2, is the main determinant of these values. Nifedipine had a preferential effect on the pulmonary circulation: pulmonary vascular resistance dropped 35%, compared to a decrease of 15% in systemic vascular resistance. Unlike the study of a smaller number of subjects by Oelz et al.[6] we found a significant decrease in systemic blood pressure, which limited the frequency of repeated 10mg dosing in four of five subjects in the longer study. Nonetheless, subjects were not posturally symptomatic at rest. While the repeated doses of nifedipine were necessary to maintain the desired effect on the pulmonary circulation (drug effect was diminishing at 30 minutes), cumulative dosing of nifedipine did not vasodilate the pulmonary bed any more than the initial single 10mg dosage. This indicates that the goal of therapy should be to produce a drug effect that is sustained, but to not hope to produce greater pulmonary vasodilation by giving higher doses. Headache was not a significant side effect of nifedipine, as it was in the Oelz study.

The increase in SaO_2% in the extended trial did not quite reach statistical significance ($p=0.06$), most likely due to the small number of subjects. An increase was clearly present in series one, although modest. Oelz et al. found a small increase in arterial PO_2 and saturation that was not significant, but they did find a significant decrease in alveolar-arterial oxygen difference after nifedipine. We had hoped to examine the time course of A-aDO_2 changes versus PAP changes to determine which came first, in order to sort out the mechanism of the increased oxygenation. Unfortunately, technical problems precluded an adequate number of reliable measurements of blood gases in our study. Careful minute by minute measurements

between the 5th and 15th minutes after administration of the drug, however, revealed that the pulmonary vasodilation began at eight to fifteen minutes, prior to any change in arterial oxygenation. Measurements of PCO_2 in our original pilot study indicated that the drug had no effect on ventilation, and Oelz confirmed this. He suggested that the small change in $SaO_2\%$ was due to lessened shunt, supported by the decreased $A\text{-}aDO_2$. The finding of pulmonary vasodilation first, and a significant inverse relationship between overall values of PAP and $SaO_2\%$ also support this view. The 10% increase in cardiac output that we observed, however, could also raise arterial oxygenation slightly, by increasing mixed venous PO_2; Oelz et al. did not report cardiac output data. It is rather curious that even 24-48 hours after continued treatment with nifedipine in the Oelz study, arterial oxgenation was not significatly improved, and much lower than well controls (SaO_2 % 68.9 $\pm$ 7.5 vs 80.7 $\pm$ 5.3%).The fact that vasodilating the pulmonary bed in HAPE does not cause a **deterioration** in oxygenation, however, as would be expected in ARDS and experimental septic shock [9] supports the view that the pulmonary hypertension is an ingredient in the pathogenesis of HAPE; i.e., the pulmonary constriction is clearly not helpful. The decrease in MPAP, it seems, would eventually produce clearing of edema fluid and normalization of SaO_2 %. The decrease of $A\text{-}aDO_2$ points to that, as does subjective improvement in the symptom score. To answer the question of whether the drug opens previously constricted and therefore dry areas of the lung, or whether it reduces the pressure gradient for flux of fluid across a leaky pulmonary capillary membrane will require further investigation.

The finding of a normal distribution of pulmonary artery pressure in subjects at 4300m was surprising. We had expected a bimodal distribution, with HAPE subjects clearly diffrentiated from well persons. Although all

HAPE subjects were in the upper range of pressures, there was considerable overlap. This may be a new finding. One particularly impressive example was a climber with HAPE who went to low altitude, recovered, and returned to the laboratory at 4300m. Her MPAP was 48mm Hg both times, yet she was completely well, with no symptoms and normal oxygenation on the second visit. Clearly, although pulmonary hypertension appears to be necessary for development of HAPE, it is not the only ingredient. Further research, rather than focusing on pulmonary hypertension, should perhaps attempt to uncover this other factor.

In summary, we found in two series of studies at high altiude, that nifedipine reduced pulmonary artery pressure and pulmonary vascular resistance 30% in subjects with high altitude pulmonary edema, and slightly increased arterial oxygenation and cardiac output. The drug was well tolerated and appeared safe, but asymptomatic postural hypotension developed in many subjects, and should remain a concern when using this drug clinically in the field. Additionally, a large survey of pulmonary pressures at high altitude demonstrated a high prevalence of asymptomatic pulmonary hypertension. The work taken together indicates that pulmonary hypertension is an essential element in the pathophysiology of HAPE, and that vasodilation may be a useful therapeutic approach, but that another unknown factor or factors are apparently necessary to produce high altitude pulmonary edema.

FUTURE WORK

The objective of this work with nifedipine was twofold: to find a medical treatment for HAPE, and to assess the role of pulmonary hypertension in the pathophysiology. Nifedipine appears to be of some value for treatment, but further work is necessary to compare this treatment with

oxygen, descent, and perhaps the combination of nifedipine and oxygen. Nifedipine needs to be studied for a longer period of time, in subjects in whom it can be ethically justified. We placed all our subjects on oxygen therapy after the three hour study was completed; our clinical judgement was that nifedipine was not nearly as beneficial as oxygen or descent.

The other avenue of future work will focus on the role of pulmonary hypertension. Possible other factors necessary for genesis of HAPE include uneven vasoconstriction that could vary in one subject on repeat exposure, a neurogenic mechanism that could increase pulmonary venous pressure or vascular permeability, or inflammation or other biochemical mediators affecting permeability. These experiments will require animal models in addition to further human investigations.

REFERENCES

1. Hackett PH; Roach RC. High altitude pulmonary edema. J Wilderness Med 1990;1:3-26.

2. Schoene RB. Pulmonary edema at high altitude: Review, pathophysiology and update. Clin Chest Med 1985;6(3):491-507.

3. Hultgren HN; Grover RF; Hartley LH. Abnormal circulatory responses to high altitude in subjects with a previous history of high altitude pulmonary edema. Circulation 1971;XLIV:759-770.

4. Menon ND. High altitude pulmonary edema. N Engl J Med 1965;273(2):66-73.

5. Hultgren HN; Lopez CE; Lundberg E; Miller H. Physiologic studies of pulmonary edema at high altitude. Circulation 1964;29:393-408.

6. Hackett PH; Greene ER; Roach RC; Feil P; Selland M. Nifedipine and hydralazine for treatment of high altitude pulmonary edema (Abstract). In: Sutton JR; Coates G; Remmers JE; Eds. Hypoxia: The Adaptations Philadelphia, PA: BC Dekker; 1990:291.

7. Oelz O; Maggiorini M; Ritter M; Waber U; Jenni R; Vock P; Bartsch P. Nifedipine for high altitude pulmonary edema. Lancet 1989;2:1241-1244.

8. Graettinger WF; Greene ER; Voyles WF. Doppler predictions of pulmonary artery pressure, flow and resistance in adults. Am Heart J 1987;113:1426-1436.

9. Brigham KL; Woolverton WC; Blake LH; Staub NC. Increased sheep lung vascular permeability caused by Pseudomonas bacteremia. J Clin Invest 1974;54:792-804.

HAPE SCORING SYSTEM

Dyspnea Score

0 No shortness of breath at rest

1 No shortness of breath at rest *AND* shortness of breath on walking

2 Mild shortness of breath at rest

3 Severe shortness of breath at rest

SaO_2% Score

0 $\geq$ 80

1 70-79

2 60-69

3 < 60

Rales Score

0 No rales

1-4 One point for each quadrant of lung field with rales

TOTAL

TABLE 1 Mean values for 12 HAPE subjects at baseline and 15 minutes after 10mg nifedipine.

	Baseline			**15 minutes**				**%Change**	
	Mean	***S.D.***	***S.E.***	***Mean***	***S.D.***	***S.E.***	***P***	***Mean***	***S.D.***
SaO2%	63.42	11.46	3.3	68.67	11.56	3.3	**<0.01**	8.73	8.90
ATET	0.29	0.06	0.0	0.38	0.04	0.0	**<0.01**	36.02	29.10
MPAP	43.05	9.82	2.8	29.62	6.08	1.8	**<0.01**	-29.64	13.22
CO	4.99	0.79	0.2	5.41	0.74	0.2	**<0.03**	9.63	13.98
CI	2.63	0.24	0.1	2.74	0.22	0.1		4.72	8.58
PVR	715.47	220.51	63.7	451.88	135.21	39.0	**<0.01**	-34.46	16.18
PVRI	414.53	133.91	38.7	287.55	78.63	22.7		-28.38	15.20
SVR	1613.93	335.26	96.8	1346.92	244.14	70.5	**<0.01**	-15.15	13.38
SVRI	940.14	257.83	74.4	815.30	153.40	44.3		-11.31	10.81
HR	86.17	8.83	2.5	89.00	8.31	2.4	**NS**	3.71	9.08
MAP	98.00	10.27	3.0	89.33	8.80	2.5	**<0.01**	-8.66	5.49
SV	58.93	13.60	3.9	61.23	9.37	2.7	**NS**	6.22	14.42

TABLE 2 Effect of repeated nifedipine dosing on mean HAPE score in five subjects with HAPE.

Time	**Baseline**	**15 min.**	**30 min.**	**60 min.**	**120 min.**	**180 min.**
SaO_2 score	1.8	2.0	1.7	1.5	1.7	1.7
Rales score	2.0	2.25	1.3	1.0	1.0	1.5
Dyspnea score	1.25	1.0	0.7	1.0	0.7	1.0
Total HAPE score	5.0	5.2	3.7	3.5	3.3	4.2

TABLE 3 Individual and mean spirometry values in HAPE subjects during extended study.

HAPE SUBJECT	MEASUREMENT	BASELINE	30 min	60 min	120 min	180 min
1	PEF	550	530	540	490	515
	FVC	3.89 (81%)	3.34	3.63	2.85	2.83
2	PEF	550	560	550	570	540
	FVC	5.18 (96%)	5.20	5.27	5.18	5.08
3	PEF	480	460	500	510	500
	FVC	2.76 (61%)	2.59	2.76	2.64	2.42
4	PEF	530	560	560	550	560
	FVC	4.84 (88%)	4.92	4.84	4.49	4.84
5	PEF	710	740	690	670	720
	FVC	4.66 (78%)	5.18	6.05	5.7	6.05 (100%)
MEAN $\pm$ SEM		564	570	568	558	567
		4.27	4.27	4.51	4.03	4.24

FIGURE LEGEND

Fig. 1. Individual data for 12 subjects in Series 1. Effect of 10mg nifedipine at 15 minutes and baseline, on SaO_2 and mean pulmonary artery pressure.

Fig. 2. Series 1. Effect of nifedipine on systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), and mean arterial pressure (MAP).

Fig. 3. Series 1. Change in stroke volume, heart rate, and cardiac output 15 minutes after nifedipine.

Fig. 4. Top: Series 2. Relationship of baseline MPAP to % change in MPAP with nifedipine over 180 minutes (extended trial). Bottom: Same data displayed for Series 1, 15 minute trial.

Fig. 5. Data from Series 2. Values of mean arterial pressure, SaO_2 and mean pulmonary arterial pressure over 180 minutes in 5 subjects with extended repeat dose nifedipine.

Fig. 6. Values of existing mean pulmonary artery pressure in 59 subjects at 4300m.

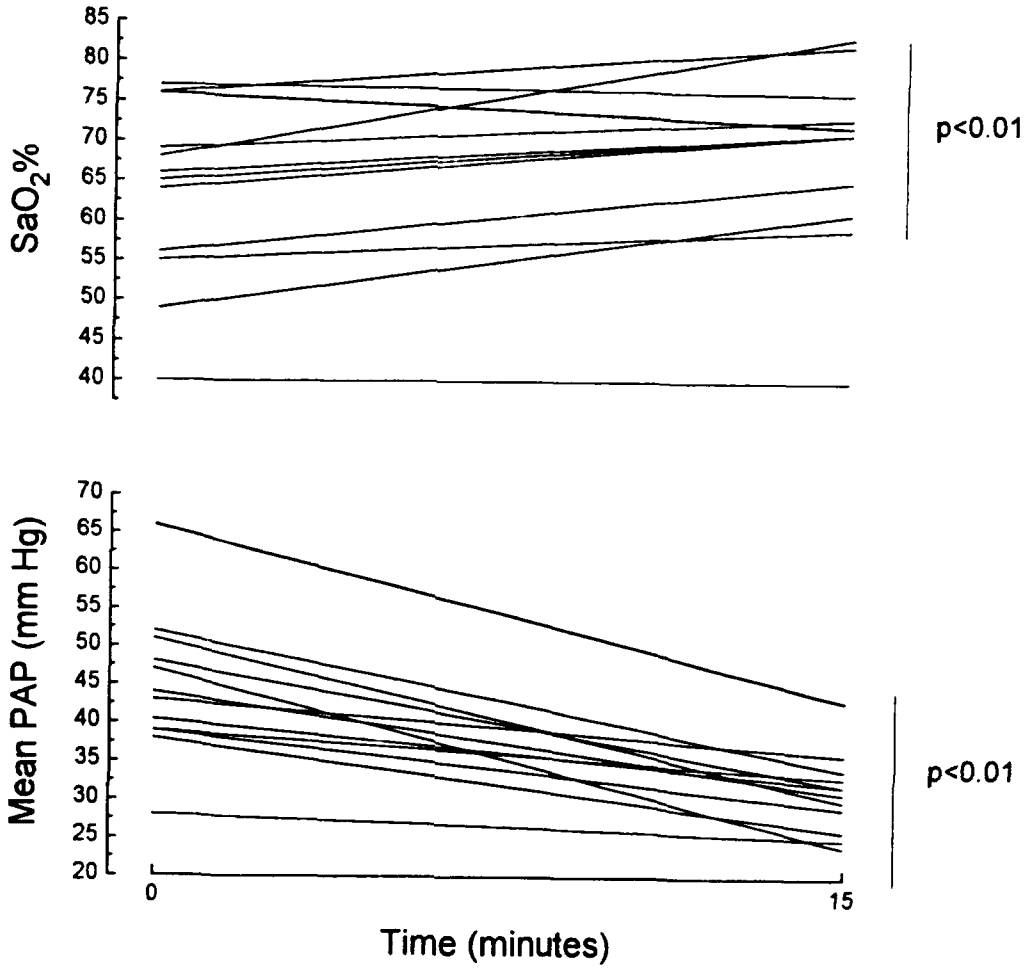

85
80
75
70
65
60
55
50
45
40
SaO_2%
p<0.01
70
65
60
55
50
45
40
35
30
25
20
Mean PAP (mm Hg)
p<0.01
0
15
Time (minutes)

FIGURE 1

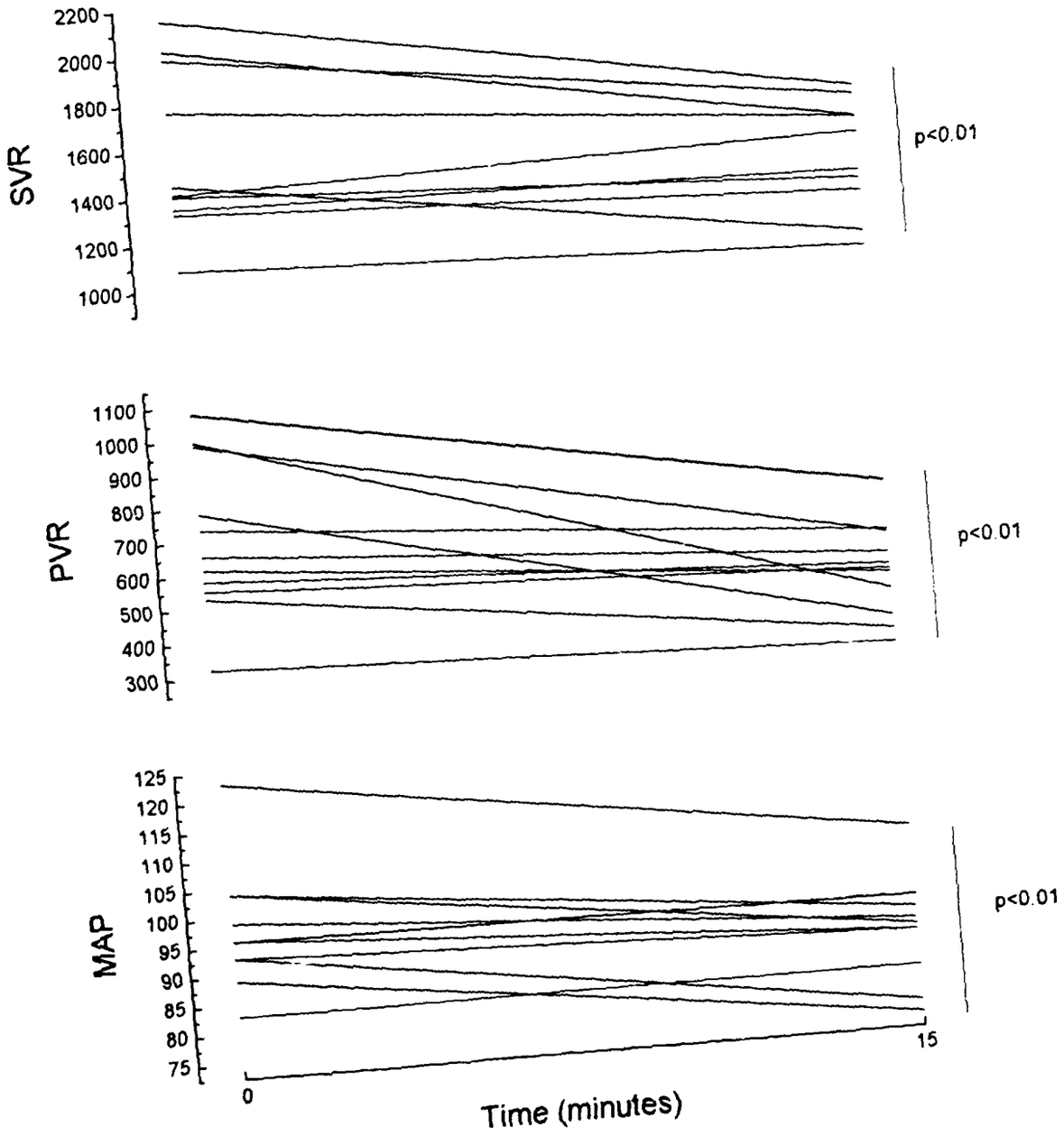

SVR
2200
2000
1800
1600
1400
1200
1000
p<0.01
PVR
1100
1000
900
800
700
600
500
400
300
p<0.01
MAP
125
120
115
110
105
100
95
90
85
80
75
p<0.01
0
15
Time (minutes)

FIGURE 2

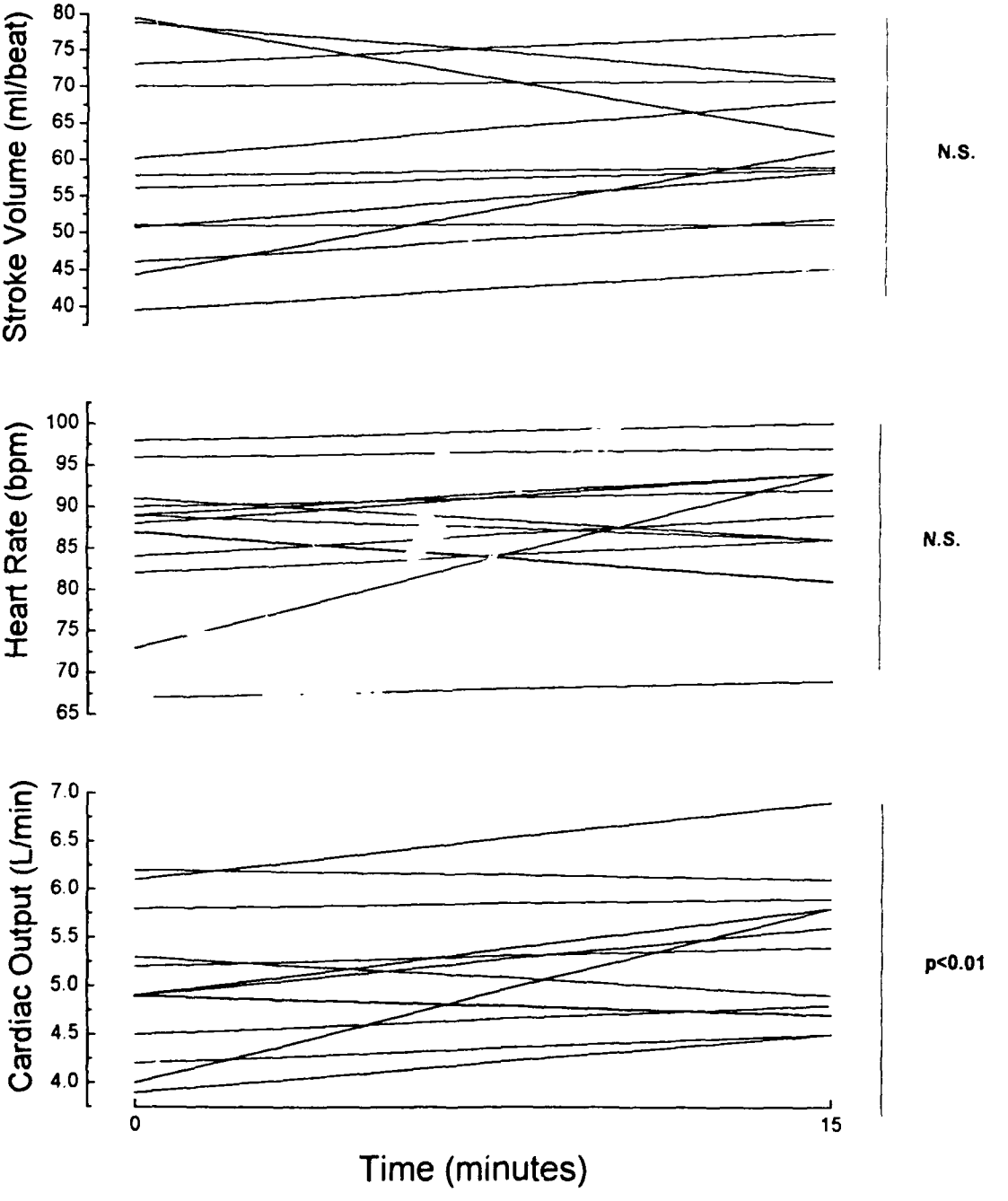

Stroke Volume (ml/beat)
80
75
70
65
60
55
50
45
40
N.S.
Heart Rate (bpm)
100
95
90
85
80
75
70
65
N.S.
Cardiac Output (L/min)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
p<0.01
0
15
Time (minutes)

FIGURE 3

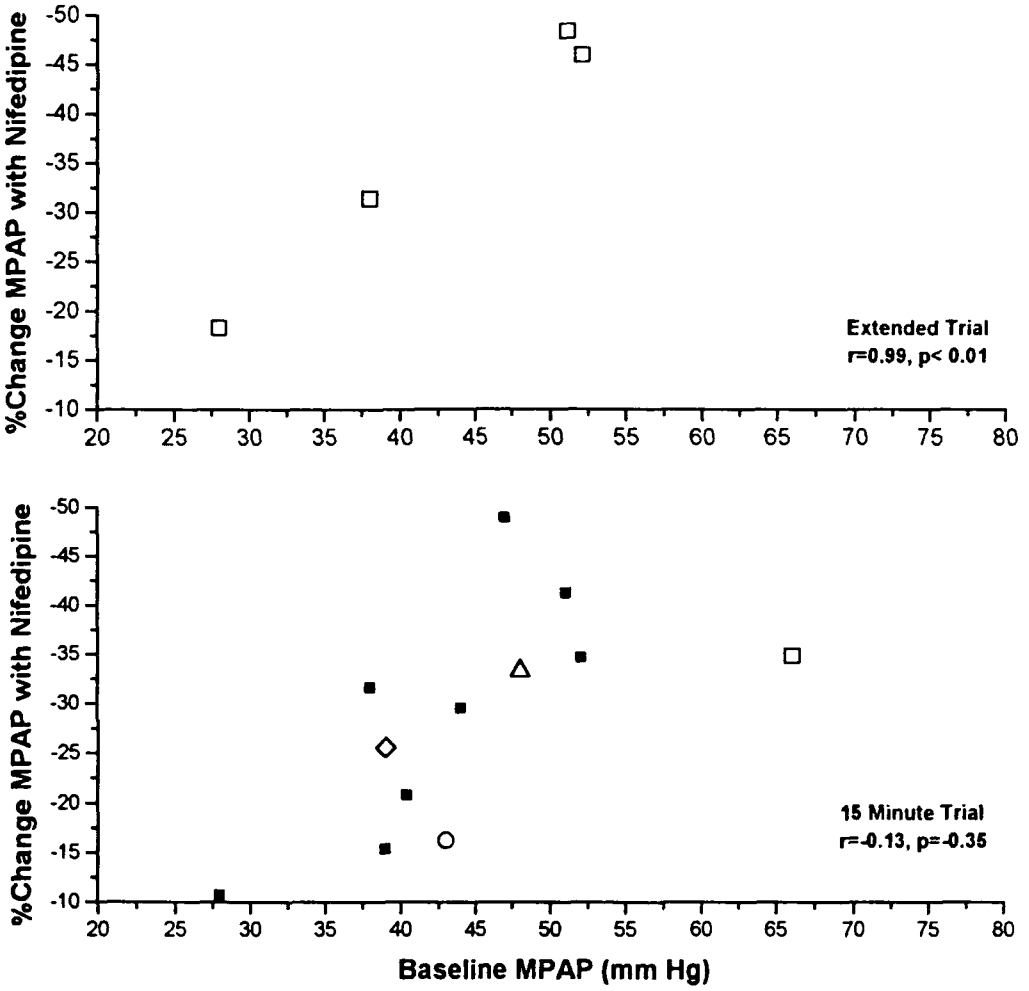

%Change MPAP with Nifedipine
-50
-45
-40
-35
-30
-25
-20
-15
-10
20
25
30
35
40
45
50
55
60
65
70
75
80
Extended Trial
r=0.99, p< 0.01
%Change MPAP with Nifedipine
15 Minute Trial
r=-0.13, p=-0.35
Baseline MPAP (mm Hg)

FIGURE 4

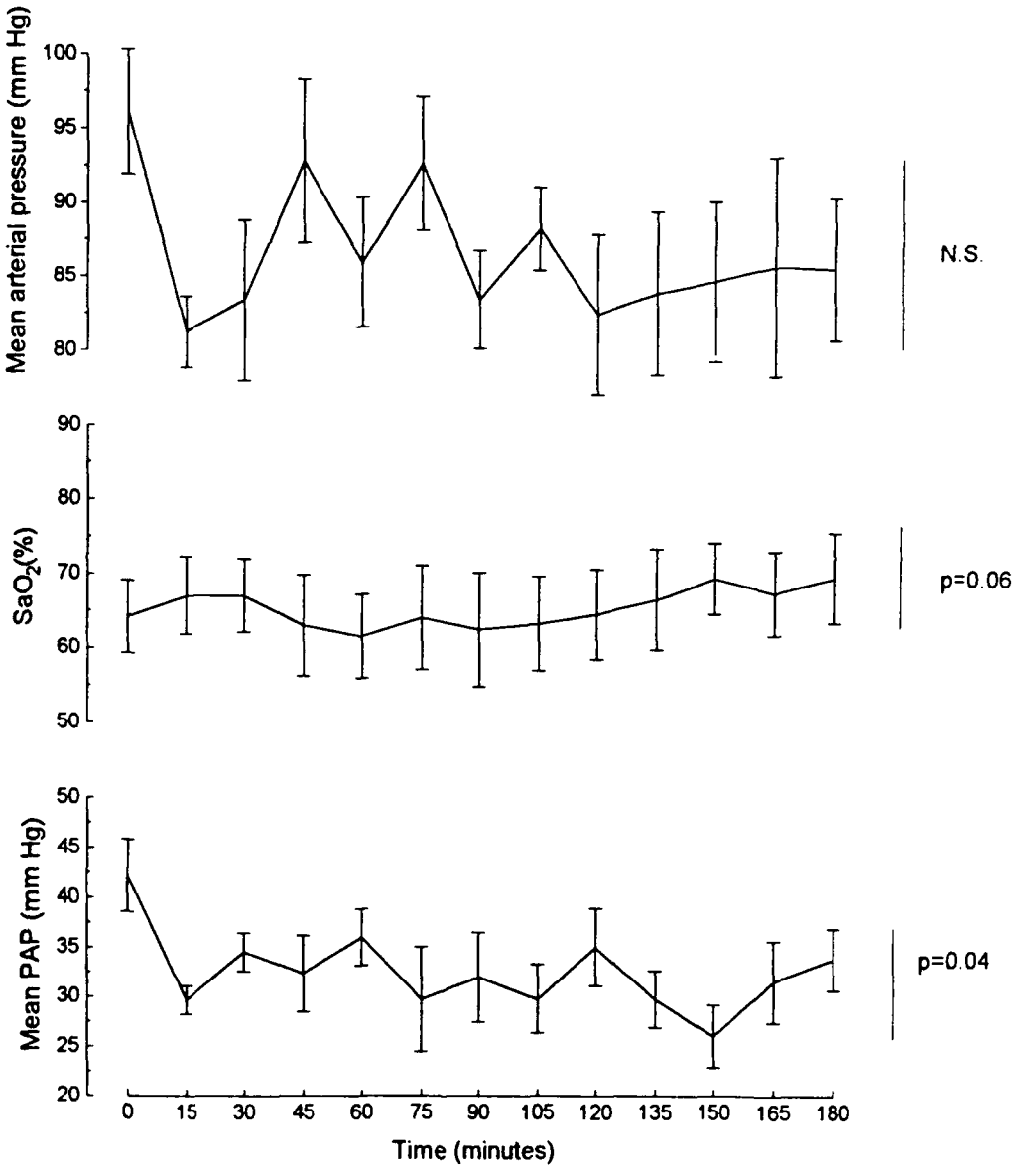

Mean arterial pressure (mm Hg)
100
95
90
85
80
N.S.
SaO_2(%)
90
80
70
60
50
p=0.06
Mean PAP (mm Hg)
50
45
40
35
30
25
20
p=0.04
0
15
30
45
60
75
90
105
120
135
150
165
180
Time (minutes)

FIGURE 5

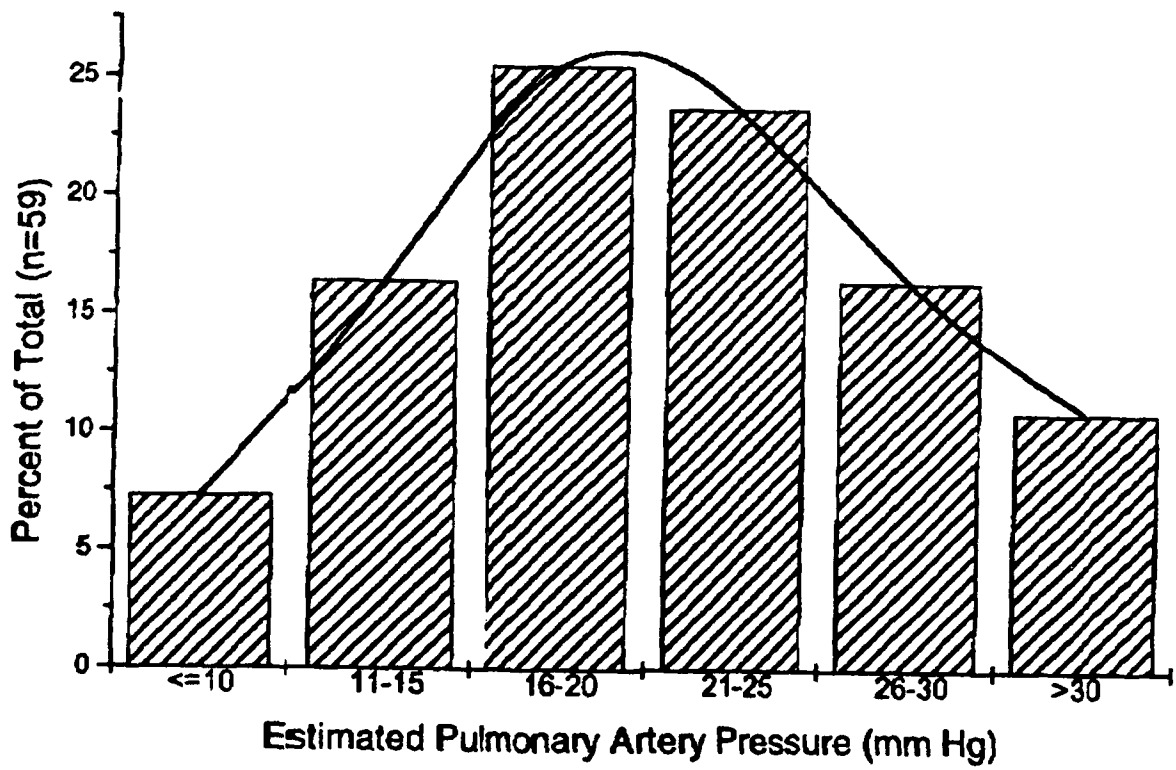

Percent of Total (n=59)
25
20
15
10
5
0
<=10
11-15
16-20
21-25
26-30
>30
Estimated Pulmonary Artery Pressure (mm Hg)

FIGURE 6